Pharmaceutical Approval Update

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**Posaconazole Oral Suspension (Noxafil)**

**Manufacturer:** Schering-Plough Corporation, Kenilworth, NJ

**Indication:** Posaconazole is indicated for the treatment of oropharyngeal candidiasis, including infections refractory to itraconazole (Sporonox, Pri Cara) and/or fluconazole (Diflucan, Pfizer). Oral candidiasis is a fungal infection of the mouth and throat caused by the yeast Candida.

This agent is also indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years of age and older who are at high risk for the development of infection because of their severely immunocompromised status. Examples include recipients of hematopoietic stem cell transplants, patients with graft-versus-host disease, and patients with hematological malignancies with prolonged neutropenia arising from chemotherapy.

**Drug Class:** This novel lipophilic triazole antifungal agent has a molecular formula of C_{17}H_{24}F_2N_3O_7, yielding a molecular weight of 700.8. Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of the enzyme lanosterol 14α-demethylase and by the accumulation of methylated sterol precursors. Posaconazole inhibits cytochrome P450 (CYP 450)-dependent 14α-demethylase in the biosynthetic pathway of ergosterol. Inhibition of this enzyme leads to an accumulation of toxic 14α-methylsterols and a depletion of ergosterol. This results in impairment of the integrity of the fungal cell membrane and blockage of cell growth and division.

**Uniqueness of Product:** Posaconazole is the first antifungal agent approved by the Food and Drug Administration for the prevention of invasive fungal infections caused by *Aspergillus* species. Posaconazole can help prevent these life-threatening infections while patients are being treated for serious conditions such as acute leukemia and graft-versus-host disease.

**Warnings:**

**Hypersensitivity:** There is no information regarding cross-sensitivity between posaconazole and otherazole antifungal agents. Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles.

**Hepatic Toxicity:** In clinical trials, there were infrequent cases of hepatic reactions, including mild-to-moderate elevations in alanine and aspartate transaminases (ALT, AST), alkaline phosphatase, total bilirubin, and clinical hepatitis. The elevated liver enzyme levels were generally reversible when therapy was discontinued; in some instances, liver function test results returned to normal without drug interruption. Discontinuation of therapy was rarely required.

In rare instances, more severe hepatic reactions (e.g., cholestasis, hepatic failure, including fatalities) were reported in patients with serious underlying medical conditions (e.g., hematological malignancy) during treatment with posaconazole. These severe hepatic events were seen primarily in patients receiving 800 mg daily (400 mg twice daily or 200 mg four times daily) for another indication.

**Monitoring of Hepatic Function:** Liver function findings should be evaluated at the start of and during the course of posaconazole therapy. Patients whose liver enzyme concentrations become abnormal during posaconazole therapy should be monitored for the development of more severe hepatic injury.

Patient management should include laboratory evaluation of hepatic function (particularly liver enzymes and bilirubin). Discontinuation of posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to this agent.

**Drug Interactions with Cyclosporine:** Cases of elevated cyclosporine levels resulting in rare serious adverse events (nephrotoxicity and leukoencephalopathy) and death were reported in clinical efficacy studies. Dose reduction and more frequent clinical monitoring of cyclosporine, tacrolimus (e.g., Prograf, Fujisawa), and sirolimus (Rapamune, Wyeth) should be performed when posaconazole therapy is initiated.

**Precautions:**

**Arrhythmias and QT Prolongation:** Some azoles, including posaconazole, have been associated with prolongation of the QT interval on the electrocardiogram (ECG). Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the corrected QT (QTC) interval. During clinical development, torsades de pointes occurred in one patient taking posaconazole. This patient was seriously ill with multiple confounding risk factors, including a history of cardiototoxic chemotherapy, hypokalemia, and concomitant medications that might have contributed to the problem.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions. It should not be taken with drugs that are known to prolong the QTc interval and that are metabolized through CYP 3A4. Rigorous attempts to correct potassium, magnesium, and calcium levels should be made before posaconazole therapy is started.

**Dosage and Administration.** Posaconazole Oral Suspension 200 mg/5 ml should be administered three times a day. A measured dosing spoon is provided, marked for doses of 2.5 ml and 5 ml. The duration of therapy is based on recovery from neutropenia or immunosuppression.

To enhance the oral absorption of posaconazole and optimize plasma concentrations:

- each dose of posaconazole oral suspension should be taken with a full meal or liquid nutritional supplement. For

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patients who cannot eat a full meal or tolerate an oral nutritional supplement, alternative antifungal therapy should be considered, or patients should be monitored closely for breakthrough fungal infections.

• patients with severe diarrhea or vomiting should be monitored for breakthrough fungal infections.

• coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefits outweigh the risks. If these drugs are necessary, patients should be monitored closely for breakthrough fungal infections.

Commentary: During the last two decades, systemic fungal infections have been recognized as a major cause of morbidity and mortality. Only a few therapeutic options are available for these infections. Posaconazole was developed to meet the increasing need for a new antifungal therapy and to address the rising incidence of invasive fungal infections and the emergence of fungal resistance. It has a broad spectrum of antifungal activity and may be beneficial for both systemic and superficial infections.

Posaconazole has shown promising clinical efficacy against life-threatening fungal infections that are often refractory to currently available antifungal therapies for invasive aspergillosis, fusariosis, and an emerging infection, zygomycosis. This agent can help prevent the development of life-threatening invasive fungal infections during therapy for serious conditions, such as acute leukemia and graft-versus-host disease.

Sources: www.schering-plough.com; www.pharmacyone-source.com

Travoprost Z Ophthalmic Sterile Solution 0.004% (Travatan Z)

Manufacturer: Alcon Laboratories, Inc., Fort Worth, TX

Indication: Travoprost Z is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of, or insufficiently responsive to, other IOP-lowering medications.

Drug Class: This agent is a synthetic prostaglandin F$_{2\alpha}$ (PGF$_{2\alpha}$) analogue. Its chemical name is isopropyl (Z)-7-[(1 R, 2 R, 3 R, 5 S)-3,5-dihydroxy-2-{(1 E, 3 R)-3-hydroxy-4-{[(α,α,α-trifluorom-toly)]oxy}-1-butanyl}cyclopentyl]-5-heptenoate.

Uniqueness of Drug: The new formulation eliminates the preservative benzalkonium chloride (BAK) from Alcon’s present Travatan solution and replaces it with Sofzia, an ionic, buffered preservative system that is gentle to the ocular surface. Alcon developed this BAK-free version because the long-term use of topical solutions containing BAK was found to irritate the ocular surface and exacerbate conditions such as dry eye. (The “Z” in the agent’s name represents zero BAK.)

Warnings: Travoprost Z has been reported to cause potentially permanent changes, such as increased pigmentation of the iris and eyelashes, darkening of the periorbital tissue (eyelid skin), and increased growth of the eyelashes.

Travoprost Z may gradually result in a change in eye color by increasing the number of melanosomes in the melanocytes of the iris. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes or deposition of pigment granules to other areas of the eye are unknown. The change in iris color occurs slowly and may not be noticeable for months to years.

Patients should be informed of the possibility of iris color change.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, of the eyelid tissue, and of the eyelashes in the treated eye; of different eye colors; and of a disparity between the eyes in length, thickness, or number of eyelashes.

Precautions:

General. Bacterial keratitis has been associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who usually had a concurrent corneal disease or a disruption of the epithelial surface.

Color Changes. Increased brown pigmentation of the iris may be more noticeable in patients with mixed colored irides (blue-brown, gray-brown, yellow-brown, or green-brown), but it has also been observed in patients with brown eyes. The color change is believed to be a result of increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown.

Typically, the brown pigmentation around the pupil spreads concentrically toward the periphery in affected eyes, but the entire iris or parts of it may become more brownish. Until more information is available, patients should be examined regularly. Depending on the situation, treatment may be stopped if increased pigmentation ensues.

Ocular Conditions. Travoprost Z should be used with caution in patients with a history of intraocular inflammation (iritis or uveitis) and generally should not be used in patients with active intraocular inflammation.

Macular edema has been reported during treatment with PGF$_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. Travoprost Z should be used with caution in these patients.

Travoprost Z has not been evaluated for the treatment of angle-closure glaucoma, inflammatory glaucoma, or neovascular glaucoma.

Kidney and Liver Impairment. Travoprost Z has not been studied in patients with renal or hepatic impairment. It should be used with caution in such patients.

Contact Lenses. Travoprost Z should not be administered while the patient is wearing contact lenses. Contact lenses should be removed before the solution is administered. The lenses may be re-inserted 15 minutes following the administration of travoprost Z.

Dosage and Administration: The recommended dosage is one drop in the affected eye once daily in the evening. The dosage should not exceed once a day, because more frequent administration may decrease the IOP-lowering effect. The reduction of IOP starts approximately two hours after administration, and the maximum effect is reached after 12 hours.

Travoprost Z may be used concomitantly with other topical ophthalmic drug products to reduce IOP. If more than one
topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

**Commentary:** Problems affecting the ocular surface are critical variables in glaucoma management. Unfortunately, for many glaucoma patients, the chronic therapy that is helping to preserve their vision also may be causing ocular irritation and exacerbating symptoms of dry eye over time. When these problems occur, patients become non-adherent to their medical regimen, or they may self-treat with over-the-counter artificial tears.

An abundance of evidence has identified concerns about changes to the conjunctiva and the cornea related to ophthalmic preservatives of IOP-lowering medications. Topical IOP-reducing agents containing BAK may negatively affect the success rates of glaucoma-filtration surgical procedures. The negative effects of BAK are cumulative in a long-term scenario of chronic use, such as in glaucoma therapy. The travoprost Z formulation preserves the preservative BAK from the original travoprost solution.

Because almost 40% of glaucoma patients have ocular-surface disease, travoprost Z is an advance in therapy that should enable physicians to address an unmet need of many glaucoma patients.

**Sources:** www.travatan.com; www.rxlist.com; www.fda.gov; www.eyeworld.org

**Arformoterol Tartrate Inhalation Solution (Brovana)**

**Manufacturer:** Sepracor, Inc., Marlborough, MA

**Indication:** Arformoterol solution is indicated for the long-term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. COPD is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function.

Arformoterol is intended for use with a nebulizer only.

**Drug Class:** As a single isomer of formoterol (Foradil Aerolizer, Schering) arformoterol is the first long-acting beta₂-adrenergic agonist bronchodilator to be developed in an inhalation solution. The agent’s molecular weight is 494.5 g/mol, and its empirical formula is C₁₉H₁₈N₂O₄ • C₄H₆O₆ (1:1 salt).

**Uniqueness of Drug:** Arformoterol is the first drug in its class to be approved as an inhalation solution for use with a nebulizer, a machine that converts liquid medication into a mist that is inhaled through a mouthpiece or mask.

**Boxed Warning:** Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. A large placebo-controlled U.S. study compared the safety of another long-acting beta₂-adrenergic agonist, salmeterol xinafoate (Serevent, GlaxoSmithKline), or placebo. When added to usual asthma therapy, salmeterol resulted in an increase in asthma-related deaths in the patients receiving it. This finding may apply to arformoterol.

**Warnings:** The risk of asthma-related death may be increased with long-acting beta₂-adrenergic agonists. Data are not available to determine whether the death rate in patients with COPD is increased by long-acting beta₂-adrenergic agonists.

Patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times daily) should discontinue the routine use of these drugs and should use them only for symptomatic relief of acute respiratory symptoms.

As with other inhaled beta₂-agonists, arformoterol can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, arformoterol should be discontinued immediately and alternative therapy should be instituted.

Like other beta₂-agonists, arformoterol can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate or blood pressure. Even though such effects are uncommon after administration of arformoterol at the recommended dose, the drug may need to be discontinued if these effects occur.

Beta-agonists have also been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST-segment depression. The clinical significance of these findings is unknown.

As with other sympathomimetic amines, arformoterol should be used with caution in the following circumstances:

- patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- patients with convulsive disorders or thyrotoxicosis
- patients who are unusually responsive to sympathomimetic amines

**Contraindications:** Arformoterol is not indicated for patients with acute episodes of bronchospasm (as rescue therapy) or for patients with acutely deteriorating COPD, which may be a life-threatening condition.

It should not be used in conjunction with other inhaled, long-acting beta₂-agonists or with other medications containing long-acting beta₂-agonists when patients are beginning treatment.

This product should not be prescribed for children.

**Dosage and Administration:** Arformoterol tartrate inhalation solution 15 mcg is administered twice daily (in the morning and evening) by nebulization as maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema.

**Commentary:** COPD is the fourth leading cause of death in the U.S. In 2004, approximately 12 million adults in the U.S. were reported to have COPD. Mortality rates for COPD have been increasing and are expected to continue to rise.

Patients who need nebulized treatment may benefit from the rapid and sustained bronchodilation that arformoterol, a long-term maintenance treatment, can provide. With the approval of this product, health care providers have a new choice in the treatment arsenal for COPD that may offer an effective and a safe way to manage bronchoconstriction associated with this disease. However, arformoterol has not been shown to have an impact on the progression of disease or survival of patients with COPD.

**Sources:** www.sepracor.com; www.brovana.com; www.quote.com